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**In Vivo Hepatic Reprogramming of Myofibroblasts with AAV Vectors as a Therapeutic Strategy for Liver Fibrosis.**

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**Authors:** Milad Rezvani, Regina Espanol-Suner, Yann Malato, Laure Dumont, Andrew A Grimm, Eike Kienle, Julia G Bindman, Ellen Wiedtke, Bernadette Y Hsu, Syed J Naqvi, Robert F Schwabe, Carlos U Corvera, Dirk Grimm, Holger Willenbring

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**Public Summary:**

This paper establishes the feasibility of in vivo hepatic reprogramming as a therapy for liver fibrosis. For this, the cells at the center of liver fibrosis, so-called myofibroblasts, are reprogrammed into hepatocytes by expression of hepatic transcription factors. The approach lends itself well to clinical translation because it uses clinically approved adeno-associated viral vectors to deliver the hepatic transcription factors.

**Scientific Abstract:**

Liver fibrosis, a form of scarring, develops in chronic liver diseases when hepatocyte regeneration cannot compensate for hepatocyte death. Initially, collagen produced by myofibroblasts (MFs) functions to maintain the integrity of the liver, but excessive collagen accumulation suppresses residual hepatocyte function, leading to liver failure. As a strategy to generate new hepatocytes and limit collagen deposition in the chronically injured liver, we developed in vivo reprogramming of MFs into hepatocytes using adeno-associated virus (AAV) vectors expressing hepatic transcription factors. We first identified the AAV6 capsid as effective in transducing MFs in a mouse model of liver fibrosis. We then showed in lineage-tracing mice that AAV6 vector-mediated in vivo hepatic reprogramming of MFs generates hepatocytes that replicate function and proliferation of primary hepatocytes, and reduces liver fibrosis. Because AAV vectors are already used for liver-directed human gene therapy, our strategy has potential for clinical translation into a therapy for liver fibrosis.

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